REMARKS

Claims 42-71 were previously pending in this application. No claims are amended, canceled, or added. Claims 44-46, 52-54, and 59-61 are withdrawn. As a result, claims 42-43, 47-51, 55-58 and 62-71 are pending for examination with claims 42, 50, 57, 64, and 70 being independent claims.

No new matter has been added.

Defective Oath or Declaration

The Examiner has objected to the Oath/Declaration because according to the Examiner the preliminary amendment includes subject matter that is not supported by the specification and drawings.

Applicants respectfully request reconsideration. A new matter rejection has not even been made against any of the claims. Thus applicants cannot address such a rejection. Each of the claims is fully supported by the disclosure of at least the parent application, US 08/960,774, in which the oath/declaration was filed, which is the same specification of the above-identified patent application. The issues of enablement and written description are addressed below.

Defective Information Disclosure Statement

The information disclosure statement filed by Applicant has been objected to under 37 CFR 1.56(b) and not considered. The Examiner has quoted CFR 1.56 (b) and then concluded that the information provided in the 46 references that she did review "do not compel a conclusion that a claim is unpatentable." Accordingly, she concluded that "the submission is not in compliance with 37 CFR 1.56 and 1.98." Applicants submit herewith a petition to request reconsideration of the IDS. The arguments are reiterated below.

Applicants assert that they have complied with their duty of disclosure as outlined in the MPEP §609 and §2001- 2004 and in compliance with 35 C.F.R. §1.56, §1.97 and §1.98. Applicants

present a clean copy of the IDS previously submitted for review by the Examiner (omitting those references that have already been considered) with a Petition for review of these references under 37 C.F.R. §1.181 and §1.182. The clean copy is updated with the format requirements now in place under 37 CFR 1.98(a)(1). Applicants request that these references be reviewed by the Examiner and be granted the date of submission of the original filed IDS.

Applicant's strongly disagree with the Examiner's refusal to consider the IDS. Initially, Applicants point out that they are in agreement that the references "do not compel a conclusion that a claim is unpatentable." If Applicants had information that compelled a conclusion that a claim was unpatentable, Applicants would not pursue such a claim.

The position taken by the Examiner in refusing to review the references set forth in the IDS is inconsistent with the Patent Office policy of requesting information. For instance, "once the minimum requirements of 37 CFR 1.97 and 37 CFR 1.98 are met, *the examiner has an obligation to consider the information*." (MPEP 609, emphasis added). Additionally, the Patent Office recognizes, and through that recognition, appears to sanction that Applicants will be submitting information that is related to the invention but that does not compel a prima facie case of unpatentability. According to MPEP 2001.05 "if information is not material, there is no duty to disclose the information to the Office. Thus, it is theoretically possible for applicants to draft claims and a specification to avoid a *prima facie* case of obviousness over a reference and then to be able to withhold the reference from the examiner. *The office believes that most applicants will wish to submit the information, however, even though they may not be required to do so, to strengthen the patent and avoid the risks of an incorrect judgment on their part on materiality or that it may be held that there was an intent to deceive the Office.*" (MPEP 2001.05, emphasis added).

Each of the references cited in the IDS submitted on January 14, 2004 was previously cited to the Patent Office in a prior application relied upon for an earlier filing date under 35 USC 120. Such information is indicated at the end of the Form 1449. According to MPEP2006.06(b) if "the application under examination is identified as a continuation , divisional, or continuation-in –part of an earlier application, the examiner will consider the prior art cited in the earlier application. See MPEP 609. The examiner must indicate in the first Office action whether the prior art in a related application has been reviewed. Accordingly, no separate citation of the same prior art need be made

in the later application." (MPEP 2001.06(b)). "The examiner will consider information which has been considered by the Office in a parent application when examining: (A) a continuation application filed under 37 CFR 1.53(b), (B) a divisional application filed under 37 CFR 1.53(b), or (C) a continuation-in-part application filed under37 CFR 1.53(b). A listing of the information need not be resubmitted in the continuing application unless the applicant desires the information to be printed on the patent." (MPEP 609.02(A)(2)) In this case, Applicant desires to have it printed on the front page of the patent. Additionally, as stated above, Applicants have submitted herewith a clean copy of the 1449 which is updated with the format requirements now in place under 37 CFR 1.98(a)(1).

Of the 46 US Patent and PreGrant Patent documents listed on the IDS and mentioned by the Examiner as being reviewed and considered to have a "low percentage... material to patentability", 16 are other patents/applications belonging to the same applicant or assignee. According to MPEP 2004 (9) applicants should bring such patents/applications to the attention of the Examiner. "Do not rely on the examiner of a particular application to be aware of other applications belonging to the same applicant or assignee. It is desirable to call such applications to the attention of the examiner even if there is only a question that they might be 'material to patentability' of the application the examiner is considering." (MPEP 2004 (9)).

The Examiner has stated that each of the non-patent publications listed on the IDS is missing the publisher and date of publication. Applicants traverse. It unclear to Applicants where the requirement of listing the publisher is found. Additionally, the dates of publication are included.

It is unclear from the rejection which section of 37 CFR 1.56, 1.97, and 1.98 with which Applicants' IDS fails to comply. "multiple information disclosure statements may be filed in a single application, and they will be considered, provided each is in compliance with the appropriate requirements of 37 CFR 1.97 and 37 CFR 1.98." (MPEP 609). Thus, Applicants request that the cited references be reviewed by the Examiner and be granted the date of submission of the original filed IDS.

Double Patenting Rejection:

Claims 42-43, 47-51, 55-58 and 62-71 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 97 of copending Application No. 10/613,524. The rejection is a provisional one since none of the claims in the 10/613,524 application has been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claims 42-43, 47-51, 55-58 and 62-71 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 37, of copending Application No. 10/894862. The rejection is a provisional one since none of the claims in the 10/894862 application has been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claims 42-43, 47-51, 55-58 and 62-71 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19, of copending Application No. 10/987146. The rejection is a provisional one since none of the claims in the 10/987146 application has been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claims 42-43, 47-51, 55-58 and 62-71 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 42, of copending Application No. 10/382822. The rejection is a provisional one since none of the claims in the 10/382822 application has been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claims 42-43, 47-51, 55-58 and 62-71 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 59, of copending Application No. 11/255100. The rejection is a provisional one since none of the claims in the 11/255100 application has been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claims 42-43, 47-51, 55-58 and 62-71 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 45, of copending Application

No. 11/361313. The rejection is a provisional one since none of the claims in the 11/361313 application has been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claim Rejections – 35 USC §112

Claims 42-43, 47-51, 55-58 and 62-71 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The Examiner has stated that "to provide adequate written description and evidence of possession, the specification *must* provide sufficient description of the claimed invention by i) actual reduction to practice, ii) reduction to drawing; or iii) disclosure of relevant identifying characteristics, such as disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, correlation between structure and function, and methods of making the claimed invention." (Office Action page 6, emphasis added). Applicants disagree that an adequate written description must be provided by the above-list. MPEP 2162 actually states:

> "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it")."

This statement is preceded by the following:

> An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. (MPEP 2163)

There is no requirement that Applicants demonstrate written description through actual reduction to practice or drawings. With respect to section iii) of the rejection related to disclosure

of relevant identifying characteristics, Applicants disagree with the Examiner's conclusions. The Examiner has stated that "the disclosure fails to provide relevant identifying characteristics relating to the claimed invention. The disclosure fails to set forth the complete structure of an oligonucleotide that treats, prevents or ameliorate papilloma viral infection." The statement is incorrect. Throughout the specification Applicants teach that the molecule useful according to the methods of the invention is a nucleic acid having an unmethylated CpG dinucleotide. In some preferred embodiments, the unmethylated CpG dinucleotide must have at least 2 nucleotides on the 5' side and the 3' side. In some preferred embodiments the nucleic acid has a stabilized backbone. Examples of numerous CpG containing nucleic acids are shown in the Tables and throughout the description. All of the structure of this class of compounds (oligonucleotides containing an unmethylated CpG dinucleotide) is set forth clearly in the description found in the specification. One of skill in the art would recognize the full scope of the class of compounds useful in the claimed method. The description adequately demonstrates Applicant had possession of the full scope of compounds.

It is further stated in the Office Action (page 8) that "The disclosure does not even set forth the partial structure of oligonucleotides containing the CpG motif to treat, prevent or ameliorate papilloma viral infection." For each of the reasons stated above, Applicants disagree. The specification adequately describes the whole structure of the oligonucleotides.

It is also stated that "the disclosure further failed to set forth the physical and chemical properties of oligonucleotides encompassed by the claimed invention." It is unclear what is meant by this statement. If the quoted statement is meant to refer to the chemical structure of an oligonucleotide, Applicants assert that it is not necessary to supply such a structure in the specification as filed. The chemical structure of oligonucleotides was well known at the time the patent application was filed. Such information could be found in numerous text books and scientific resources. It is not necessary for Applicants to include such information in the specification as filed.

Finally, it is concluded that "Furthermore, the disclosure failed to set forth any functional characteristics that oligonucleotides containing the CpG motif must possess to treat, prevent or ameliorate papilloma viral infection." Applicants are not aware of a requirement for the

specification to set forth "functional characteristics" of a compound in order to meet the written description requirement. Applicants have taught in the specification that a class of compounds can be used to treat viral disease. Applicants have fully described the structure of the class of compounds, methods for making the class of compounds, methods for administering the class of compounds and the types of viral disease, including papilloma virus, that could be treated. It is unclear what functional characteristics are missing.

Applicants have demonstrated possession of a class of compounds (oligonucleotides containing an unmethylated CpG dinucleotide) which can be used according to the methods of the invention. It is respectfully requested that the rejection be withdrawn.

Claims 42-43, 47-51, 55-58 and 62-71 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The Examiner has presented a rejection based on the Wands factors. Each of the specific rejections is addressed separately by Applicants below.

Breadth of the Claims

The claims cover the treatment of papilloma virus infection using CpG oligonucleotides. The dependent claims contain additional structural limitations on the CpG oligonucleotide. The CpG must include an unmethylated CpG. In some embodiments the CpG dinucleotide is flanked by specific nucleotides, e.g., a 5' T. In other embodiments multiple CpG dinucleotides are included in the nucleic acid.

Presence or absence of working examples:

The Examiner has stated that the specification does not contain any working examples directed to the claimed invention of use of an oligonucleotide containing the CpG motif in treating, preventing or ameliorating papilloma viral infection. "Nothing exists in the specification demonstrating that fundamental research has been conducted to support Applicants' claim, wherein oligonucleotides comprising the CpG motif treat, present, or ameliorate viral infection including papilloma viral infection."

Applicants have demonstrated that oligonucleotides containing unmethylated CpG motifs are effective in inducing a pattern of immune stimulation that is consistent with the treatment of

viral infection. Applicants have provided examples in the specification that show production of antibody in response to oligonucleotide stimulation (Example 2), stimulation of B cells, natural killer (NK) cells and monocytic cells (Example 3, Example 4, Example 11, Figure 6 and Figure 11), and production of IFNγ (Figure 15) as well as other cytokines. The specification asserts that CpG oligonucleotides are useful in treating viral infections, including papilloma viral infections. The combination of the changes in immune parameters demonstrated with CpG oligonucleotides is sufficient to support applicants assertion at the time of the invention that CpG oligonucleotides would be useful in the treatment of papilloma viral infection. Applicants assert that a correlation between CpG and their use in the treatment and/or prevention of viral infection is disclosed and enabled.

Applicants strongly object to the examiner's assertion that "Nothing exists in the specification demonstrating that fundamental research has been conducted to support Applicants' claim". In fact, Applicants specification describes the fundamental research related to the discovery that CpG oligonucleotides are useful in treating viral infection. Many other researchers have begun to work in the field, following Applicants' discovery.

Amount of direction or guidance presented:

Applicants have provided sufficient direction and guidance in the specification. Applicant has described the structural properties of CpG oligonucleotides and have taught that they can be used to treat viral infection including papilloma viral infection. Further Applicants have provided preferred modes of administration and formulations. Those of skill in the art are well aware of such routine methods of formulating and administering drugs.

The Examiner has asserted that "all that is present in the specification are conjectures of potential application of such oligonucleotides". The Examiner's conclusion is inaccurate and unsupported by the evidence. The term "conjecture" is defined in Webster's Ninth New Collegiate dictionary as "a conclusion deduced by surmise or guesswork." One of skill in the art would recognize the utility of treating viral infections was well supported based on the data and description described in the specification. In fact numerous investigators have begun research in the area of CpG oligonucleotides following the fundamental discovery by the instant inventors that this class of oligonucleotides having a CpG motif were immune stimulatory. The Examiner is requested to

provide evidence to support her statement that the claimed invention is based on surmise or guesswork.

Nature of the invention

The invention is directed to a method of treating, preventing or ameliorating papilloma viral infection using a class of CpG containing oligonucleotides having structural requirements. The Examiner has stated that the invention is "directed to the use of the art recognized immunostimulatory activity of oligonucleotides containing the CpG motif." Applicants reiterate on the record, that the discovery that oligonucleotides containing the CpG motif were immunostimulatory and thus useful for treating viral infection, is the invention of Applicants. The invention is not simply a use of some previously discovered art recognized class of compounds known for having a particular activity.

State of the Art

The Examiner has made several statements about the state of the art. In order to address each statement, Applicants have copied the Examiner's statement and provide comments immediately below.

- "The art acknowledges the importance of Th1 type immune response, which is stimulated by the production of Th1 cytokines, in the elimination of intracellular pathogens, including viruses. However, the art has not accredited or recognized any one particular Th1-assoicated cytokine to the treatment, prevention, and amelioration of viral infection in a subject. Specifically, the art teaches that while cytokines secreted by T helper cells are of critical importance for the outcome of many infectious disease, the production of the "right" set of cytokines can be a matter of life or death." (Office Action page 11)
  - The statement is not relevant to the claimed invention. Applicants are not exogenously administering specific cytokines. The claimed invention relates to the delivery of an oligonucleotide which stimulates in vivo the promotion or inhibition of cytokine production. The body decides which cytokines to induce or suppress in response to the administration of the oligonucleotide.
- "Specifically, Infante-Duarte et al. teaches that a tight control over where and when Th1 and Th2 immune responses happen is necessary to keep intracellular infections under control,

and to prevent the Th1 type immune response from causing damage to the host. Hence, while the importance of a Th1 type immune response is well recognized in the art, the art further notes that a balance between Th1 and Th2 type immune responses is necessary to resolve an infection." (Office Action page 11-12)

- This teaching is not inconsistent with the claimed invention. The patent application teaches that CpG oligonucleotides promote an immune response when administered in vivo. The immune response involves a shift in the balance of Th1 and Th2 cytokines such that the Th1 response is favored. The shift is a natural one that occurs in response to a stimulus that Applicants believe a naturally existing stimulant, bacterial DNA. It is believed that CpG containing oligonucleotides mimic bacterial DNA in their ability to promote an immune response. The inventors believed they discovered one of natures pathways fundamental to the immune system. This discovery is described on pages 45-46 of the specification under the heading "Teleological Basis of Immunostimulatory Nucleic Acids." It is taught that the stimulatory CpG motif, identified according to the invention, is common in microbial genomic DNA, but quite rare in vertebrate DNA. Experiments described in Example 3, in which methylation of bacterial DNA with CpG methylase was found to abolish mitogenicity, demonstrated that the difference in CpG status is the cause of immune stimulation by bacterial DNA. The resultant immune response is a natural one. Not one that is dramatically skewed to cause tissue damage.

- "The cytokine art also provided that the efficacy of Th1 associated cytokines, such as interleukin 2, interleukin 12, and interleukin 18, against intracellular pathogens are controversial, as evidenced by Aoki et al, Bohn et al, Sakao et al, Zaitseva et al and Masihi, K. Aoki et al teaches that while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2 does not confer protection for virulent *M. bovis* infection." (Office Action page 12)
  - The statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Additionally, the claimed invention relates to the delivery of an oligonucleotide which stimulates a pattern of cytokine production, not simply a

single cytokine, such as IL-2, IL-12, or IL-18. Additionally, the Aoki et al reference cited by the examiner actually teaches that cytokines have promise in the treatment of infectious disease. On page 231 2nd column it is concluded that "Undoubtedly, in the next several years we may witness the formal introduction of cytokines or their inhibitors to routine clinical use for infectious diseases other than viral hepatitis." and "Cytokines hold great promise to be used as therapeutics or immune adjuvant for vaccination against infectious disease.....Several cytokines have been successfully used for human conditions and it is anticipated that more will enter into clinical applications."

- "Interleukin-12, a Th1 associated cytokine, induces different effector mechanisms that result in either protection or exacerbation of a disease. Specifically, Bohn et al. notes that the administration of exogenous interleukin 12 confers protection against Yersinia enterocolitica in susceptible BALB/c mice, but exacerbates yersiniosis in resistant C57BL/6 mice." (Office Action page 12)
  - Again, the statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Additionally, the claimed invention relates to the delivery of an oligonucleotide which stimulates a pattern of cytokine production, not simply a single cytokine such as IL-12.
- "Interleukin 18, a Th1 associated cytokine, is responsible for the progression of endotoxin-induced liver injury in mice primed with interleukin 18." (Office Action page 12-13)
  - The statement is not relevant to the claimed invention. Applicants are not directly administering IL18. Administering a compound is very different than stimulating the body to produce the compound endogenously.
- "Both Interleukin 6 and interferon gamma augment the susceptibility of monocyte-derived macrophages to infection." (Office Action page 13)
  - The statement is not relevant to the claimed invention. Applicants are not directly administering IL6 and IFN-gamma. Administering a compound is very different than stimulating the body to produce the compound endogenously.

- "Interleukin 2 increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies." (Office Action page 13, citing Masihi)
    - The statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine and are not treating HIV Administering a compound is very different than stimulating the body to produce the compound endogenously. This point is clarified in the Masihi reference itself. In his review article Masihi describes several classes of molecules and how they are used for fighting infection. One section (section 3) is on the exogenous administration of cytokines as therapeutic agents. This is the section cited by the Examiner which describes some of the troubles associated with exogenous administration of cytokines. The next section (section 4) describes synthetic and natural immunomodulators. Section 4.1 is dedicated to CpG oligonucleotides. Unlike all of the problems highlighted by Masihi related to cytokines, Masihi describes studies in which CpG ODN were demonstrated to protect against *Listeria moncytogenes* and *Francisella tularensis* in mice. Additionally studies are described relating to successful protection against *Trypansoma Cruzi* and *Leishmania major.* The author even concludes "CpG-ODN were even curative when given after lethal *Leishmania major* infection. (page 647 1st full sentence).

Based on the above assertions, the Examiner concludes that "the art teaches that cytokines can be inherently toxic, have unclear pharmacological behavior, and also have pleiotropic effects. Hence, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated" (Office Action page 13) None of the above-statements support the above conclusions. In each instance but one (the one referring to Infante-Duarte et al.) the Examiner is describing a system of one or more exogenously administered cytokines. Applicants have not claimed the administration of cytokines. Applicants claims are directed to the administration of oligonucleotides which produce a shift in the balance of cytokine production and cellular activation in a natural environment. The body controls how much of a particular cytokine to produce. The

effect is different from administering cytokines. The ability to stimulate an immune response without directly administering immune factors such as cytokines is an advantage of the invention. The teachings of Infante-Duarte et al. cited by the Examiner are not inconsistent with the claimed invention and also don't support the above-conclusion.

Additionally, the Examiner has cited several teachings in the CpG art. Applicants address each of these below.

- "The recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 associated cytokines. However, Mutwiri et al provides that TLR-9 has only been identified in mice and humans. Mutwiri et al also provides that the TLR-9 is differentially expressed in humans and mice. Hence, if the recognition of the CpG motif were dependent of TLR-9 then it would logically follows that the extent of the Th1 type immune response induced by the oligonucleotide would necessarily vary from one species to the next." (Office Action page 14-15, citing Mutwiri et al)
  - Mutwiri et al actually state "TLR9 has yet to be identified in species other than human and mice, *but it is assumed that a similar signaling mechanism is involved in other species*". (Emphasis added) The Examiner's conclusion that the absence of TLR9 in some species would lead to variability in results is misplaced. The reference does not teach that TLR9 is absent is some species. Additionally the reference is a review article describing studies that have examined the effects of CpG therapies in a variety of animals, including mice, humans, cattle, sheep, pigs, horses, goats, rabbits, fish, dogs, cats, and chickens (see for instance page 90 first full paragraph of left column and first 20 lines of right column). The authors conclude in that paragraph in the right column of page 90 that "Together, these data suggest that in vitro stimulation of cells by CpG motifs is conserved across species, and that the enhanced activity of GACGTT in laboratory animals may be an artificial bias due to inbreeding."

- "Each oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides

varies. Krieg et al particularly notes that the type of cytokine stimulation stimulated by oligonucleotides containing CpG motifs is distinct from one oligonucleotide to the next. Additionally, both Krieg et al and Mutwiri et al note that the level and type of immune stimulation varies depending on i) the specific nucleic acids, purines and pyrimidines, surrounding the CpG motif, ii) the spacings between CpG motifs iii) the numbers of CpG motifs in an oligonucleotide; iv) the absence or presence of a CpG motif to the end of the oligonucleotide; and v) the context in which the CpG motif is presented in the sequence." (Office Action page 13-14)

- Applicants have described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject results in an aspect of the immune response being altered, with a Th1 response being favored. This class of oligonucleotides is described throughout the specification and their ability to produce a Th1 favored immune response and be used to treat disease is not only described (e.g., see page 8, lines 9-14 and page 55-56) but data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention. The fact that there is some variability in the responses depending on the sequence of the oligonucleotide is not surprising. If one were proceeding in a clinical trial one would have to select a single oligonucleotide to use. However, this is not the standard for enablement. Variability with drugs in humans is not unusual. Humans are an outbred population, genetically diverse, and humans respond with great variability to drugs. This is particularly the case where the immune system is involved. Humans have an immune status that fluctuates much more than the mice used in experimental research. A human's immune status on any particular day can determine the human's response to a drug.

- "The CpG art further teaches that the immunostimulatory activity of oligonucleotides containing the CpG is species specific, as evidenced by Mutwiri et al. Table 1 of Mutwiri et al. provides that the *in vitro* immunostimulatory activity of oligonucleotides containing

the CpG motif varies from one species to the next. Mutwiri et al. also notes that the level of immunostimulating induced by a particular oligonucleotide is also dependent on the sequence(s) flanking the CpG motif. Specifically Mutwiri et al, notes that the GTCGTT motif, which is the optimal motif for humans, is optimal for stimulation of lymphocyte proliferation in several species including cattle, sheep, goats, horses, pigs, dogs, cats and chickens; whereas the murine CpG motif (GACGTT) is only optimal for inbred rabbits and mice." (Office Action page 14, citing Mutwiri et al)

- The statement does not provide support for lack of enablement. Simply because one embodiment might be optimal or preferred does not make other embodiments non-enabled. Additionally, the statement taken from Mutwiri et al reflects the analysis of data from several published articles. It does not purport to analyze each and every CpG ODN.

- "The in vitro immunostimulatory activity of oligonucleotides containing the CpG is very species specific." (Office Action page 14, citing Mutwiri et al)
  - As described above, variability is expected. However, it has been described in the specification and confirmed in numerous references that CpG containing oligonucleotides stimulate an immune response. The consistent effect is attributed to the presence of the unmethylated CpG motif in the oligonucleotide.

The Examiner has also recited teachings from Equils and Agrawal relating to the use of CpG treatment for HIV infection. Equils describes a research study in which increased HIV replication was observed in mouse spleen cells treated with CpG ODN. Agrawal is a comment on the Equils article and is followed by a reply by Equils. The last sentence of Equils reply provides a succinct summary of the state of the art at the time of these discussions. "However the biological significance of these transient increases in HIV replication is yet to be determined." The observation by Equils (and limitations of those observations in terms of dosages and timing as described by Agrawal) are preliminary and do not rule out the use of CpG in the treatment of HIV infection. Additionally, the instant claims are directed to a method of treating papilloma virus infection, not HIV. Such post-filing references do not establish a lack of enablement.

Olbrich et al was cited for the teaching that CpG treatment "accelerated and increased the severity of Friend retrovirus in mice." (Office Action page 15). Olbrich discovered that the timing of administration of the CpG oligonucleotides was an important factor in determining the results of the treatment with CpG for retrovirus infection. Olbrich et al reported that pretreatment with CpG ODN did not induce resistance to type C retrovirus challenge, in contrast to other reports that pretreatment with CpG did induce resistance to challenge with tumor cells, Leishmania, and HSV (page 10662, 1st column). Optimization of timing protocols is expected. It does not undermine the fundamental discovery made by Applicants that CpG ODN are useful for treating infectious disease. Some inoperative embodiments are allowed within a claim. In fact Olbrich et al concluded in the last sentence of the paper that "If used under the right conditions, CpG-ODN should be a powerful substance for antiviral therapy in the future." Again the instant claimed invention is directed to the treatment of papilloma virus infection.

Thus, none of the references or passages cited by the Examiner support a conclusion of the lack of enablement of the claimed invention.

Predictability or unpredictability of the art:

The Examiner has concluded that use of cytokines and oligonucleotides containing CpG motifs in the treatment of viral disease is unpredictable. Applicants disagree. Applicants have addressed each statement by the Examiner from the prior art which was put forth to support this conclusion of lack of predictability. The variability observed with CpG oligonucleotides is not sufficient to demonstrate unpredictability. It simply shows that some oligonucleotides work better than others at stimulating the immune response. Applicants have identified the key structural property, the unmethylated CpG dinucleotide, that allows this class of oligonucleotides to function through TLR9 to stimulate an immune response that is useful in the treatment of viral infection.

Quantity of experimentation necessary:

The Examiner has provided several reasons for why additional experimentation would be necessary. For instance it is stated in the Office Action that "Applicant has not provided much, if any, guidance or direction relating to the claimed invention." It is unclear how this translates to a

finding of extensive experimentation. Applicants have taught how to make the CpG ODNs using routine methods known in the art. Applicants have also taught that they produce a pattern of immune stimulation and that they can be administered for the treatment of viral infection. One of skill in the art would simply need to make the ODN or buy it and administer it to a subject having a papilloma viral infection. The skilled artisan would know the best routes of administration to use depending on the subject. The issue of whether a drug is safe and effective in humans such that it should be approved for the use of treating humans is for the FDA to decide, not the Patent Office.

The Examiner has also stated "All that Applicant has provided is a conclusion that is made on the basis of generalized concepts that are well known in the art." The Examiner is requested to provide a basis for this assertion. Which "generalized concepts that are well known in the art" have Applicants used to base their invention on? If the Examiner is referring to the "art recognized" use of CpG oligonucleotides for stimulating an immune response, such an assertion is misplaced. This is the basis of the invention claimed herein. It is not an art recognized concept. If the Examiner is referring to something else, she should provide details. Applicants cannot find any mention of generalized concepts well known in the art described in this office action that would support such a conclusion.

Further, the Examiner has stated "And the formation of a conclusion based on generalized concepts renders the conclusion flawed." (Office Action page 17) It is not clear to the Applicants, what this statement means. As far as Applicant can tell, not only is this statement irrelevant, it is incorrect.

In view of the teaching of the instant application and the state of the art at the time of filing, Applicants submit that the claimed invention can be practiced without undue experimentation. Applicants have provided CpG oligonucleotide sequences that stimulate an immune response (and demonstrated a number of immune parameters *in vivo* and *in vitro*) and have provided guidance to one of ordinary skill in the art to use the CpG oligonucleotides to treat or prevent a viral infection. Based on the teachings in the specification one skilled in the art would have predicted that CpG is capable of treating viral infection. Numerous references, including those cited by the Examiner, have shown that CpG oligonucleotides can overcome infection, suggesting that CpG ODN is

effective in treating viral infection. Therefore, the amount of experimentation required to practice the invention is not undue.

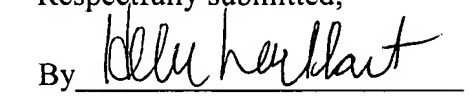
Accordingly, withdrawal of the rejection of claims 42-43, 47-51, 55-58 and 62-71 under 35 U.S.C. § 112, first paragraph is respectfully requested.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: March 30, 2007

Respectfully submitted,

By 

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